

Claims

1. A compound of formula I,



wherein

R^1 represents $-R^3$ or $-A^1C(O)N(R^4)R^5$ or $-A^1C(O)OR^4$;

A^1 represents C_{1-5} alkylene;

R^2 (which replaces one of the hydrogen atoms in the amidino unit of Pab-H) represents OH, $OC(O)R^6$, $C(O)OR^7$ or $C(O)OCH(R^8)OC(O)R^9$;

R^3 represents H, C_{1-10} alkyl, or C_{1-3} alkylphenyl (which latter group is optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy, nitro or halogen);

R^4 and R^5 independently represent H, C_{1-6} alkyl, phenyl, 2-naphthyl or, when R^1 represents $-A^1C(O)N(R^4)R^5$, together with the nitrogen atom to which they are attached represent pyrrolidinyl or piperidinyl;

R^6 represents C_{1-17} alkyl, phenyl or 2-naphthyl (all of which are optionally substituted by C_{1-6} alkyl or halogen);

R^7 represents 2-naphthyl, phenyl, C_{1-3} alkylphenyl (which latter three groups are optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy, nitro or halogen), or C_{1-12} alkyl (which latter group is optionally substituted by C_{1-6} alkoxy, C_{1-6} acyloxy or halogen);

R^8 represents H or C_{1-4} alkyl; and

R^9 represents 2-naphthyl, phenyl, C_{1-6} alkoxy or C_{1-8} alkyl (which latter group is optionally substituted by halogen, C_{1-6} alkoxy or C_{1-6} acyloxy); provided that when R^1 represents R^3 , R^3 represents benzyl, methyl, ethyl, *n*-butyl or *n*-hexyl and R^2 represents $C(O)OR^7$, then R^7 does not represent benzyl;

or a pharmaceutically-acceptable salt thereof.

2. A compound of formula I, as defined in Claim 1, wherein A^1 represents C_{1-3} alkylene when R^1 represents $-A^1C(O)N(R^4)R^5$.

3. A compound of formula I, as defined in Claim 1 or Claim 2, wherein R^4 represents H or C_{1-6} alkyl when R^1 represents $-A^1C(O)N(R^4)R^5$.
4. A compound of formula I, as defined in any one of Claims 1 to 3, wherein R^5 represents C_{1-6} alkyl or C_{4-6} cycloalkyl when R^1 represents $-A^1C(O)N(R^4)R^5$.
5. A compound of formula I, as defined in any one of Claims 1 to 3, wherein R^4 and R^5 together represent pyrrolidinyl when R^1 represents $-A^1C(O)N(R^4)R^5$.
6. A compound of formula I, as defined in any one of Claims 2 to 5, wherein A^1 represents C_{1-3} alkylene, and R^4 represents H or C_{1-3} alkyl and R^5 represents C_{2-6} alkyl or C_{5-6} cycloalkyl, or R^4 and R^5 together represent pyrrolidinyl.
7. A compound of formula I, as defined in Claim 1, wherein A^1 represents C_{1-3} alkylene when R^1 represents $-A^1C(O)OR^4$.
8. A compound of formula I, as defined in Claim 1 or Claim 7, wherein R^4 represents C_{1-6} alkyl when R^1 represents $-A^1C(O)OR^4$.
9. A compound of formula I, as defined in Claim 7 or Claim 8, wherein A^1 represents C_{1-3} alkylene and R^4 represents C_{1-4} alkyl.
10. A compound of formula I, as defined in Claim 1, wherein R^3 represents H, C_{1-10} alkyl (which latter group may be linear or, when there are a sufficient number of carbon atoms, may be branched and/or be partially cyclic or cyclic), or C_{1-3} alkylphenyl (which latter groups is optionally substituted, may be linear or, when there are a sufficient

number of carbon atoms, be branched), when R^1 represents R^3 .

11. A compound as claimed in Claim 1 or Claim 10, wherein R^1 represents H, linear C_{1-10} alkyl, branched C_{3-10} alkyl, partially cyclic C_{4-10} alkyl, C_{4-10} cycloalkyl, optionally substituted linear C_{1-3} alkylphenyl, optionally substituted branched C_3 alkylphenyl.

12. A compound as claimed in Claim 11, wherein R^1 represents linear C_{1-6} alkyl, C_{6-10} cycloalkyl, or optionally substituted linear C_{1-3} alkylphenyl.

13. A compound of formula I, as defined in any one of Claims 1 to 12, wherein R^2 represents OH.

14. A compound of formula I, as defined in any one of Claims 1 to 12, wherein R^6 represents optionally substituted phenyl or C_{1-17} alkyl (which latter group may be linear or, when there are a sufficient number of carbon atoms, may be branched, be cyclic or partially cyclic, and/or be saturated or unsaturated) when R^2 represents $OC(O)R^6$.

15. A compound as claimed in Claim 14 wherein R^6 represents optionally substituted phenyl, linear C_{1-4} alkyl, branched C_{3-4} alkyl or *cis*-oleyl.

16. A compound as claimed in Claim 15 wherein R^6 represents linear C_{1-3} alkyl or branched C_3 alkyl.

17. A compound of formula I, as defined in any one of Claims 1 to 12, wherein R^7 represents optionally substituted phenyl, C_{1-12} alkyl (which latter group is optionally substituted, may be linear or, when there are a sufficient number of carbon atoms, may be branched, cyclic or partially cyclic, and/or saturated or unsaturated), or C_{1-3} alkylphenyl (which latter

group is optionally substituted, may be linear or, when there are a sufficient number of carbon atoms, may be branched) when R^2 represents $C(O)OR^7$.

18. A compound as claimed in Claim 17 wherein R^7 represents optionally substituted and/or optionally unsaturated linear C_{1-4} alkyl or optionally substituted and/or optionally unsaturated branched C_{3-4} alkyl, optionally substituted phenyl, or optionally substituted linear C_{1-3} alkylphenyl or optionally substituted branched C_3 alkylphenyl.

19. A compound as claimed in Claim 18 wherein R^7 represents optionally substituted linear C_{1-4} alkyl or optionally substituted branched C_{3-4} alkyl, optionally substituted linear C_{1-3} alkylphenyl or branched C_3 alkylphenyl.

20. A compound of formula I, as defined in any one of Claims 1 to 12, wherein R^8 represents H or methyl, when R^2 represents $C(O)OCH(R^8)OC(O)R^9$.

21. A compound of formula I, as defined in any one of Claims 1 to 12 or Claim 20, wherein R^9 represents phenyl, or C_{1-8} alkyl (which latter group is optionally substituted, may be linear or, when there are a sufficient number of carbon atoms, may be branched and/or cyclic or partially cyclic) when R^2 represents $C(O)OCH(R^8)OC(O)R^9$.

22. A compound of formula I, as defined in Claim 20 or Claim 21 wherein R^8 represents H or methyl and R^9 represents phenyl, C_{5-7} cycloalkyl, linear C_{1-6} alkyl, branched C_{3-6} alkyl or partially cyclic C_{7-8} alkyl.

23. A compound as claimed in Claim 22 wherein R^8 represents H and R^9

represents C_{5-7} cycloalkyl, linear C_{1-6} alkyl or partially cyclic C_{7-8} alkyl.

24. A compound as claimed in any one of the preceeding claims wherein, when R^1 represents R^3 and R^3 represents optionally substituted C_{1-3} alkylphenyl, the optional substituent C_{1-6} alkyl.

25. A compound as claimed in Claim 24 wherein the substituent is methyl.

26. A compound as claimed in any one of the preceeding claims wherein, when R^2 represents $C(O)OR^7$ and R^7 represents optionally substituted C_{1-12} alkyl, the optional substituent is selected from halogen and C_{1-6} alkoxy.

27. A compound as claimed in Claim 26 wherein the substituent is selected from chloro and methoxy.

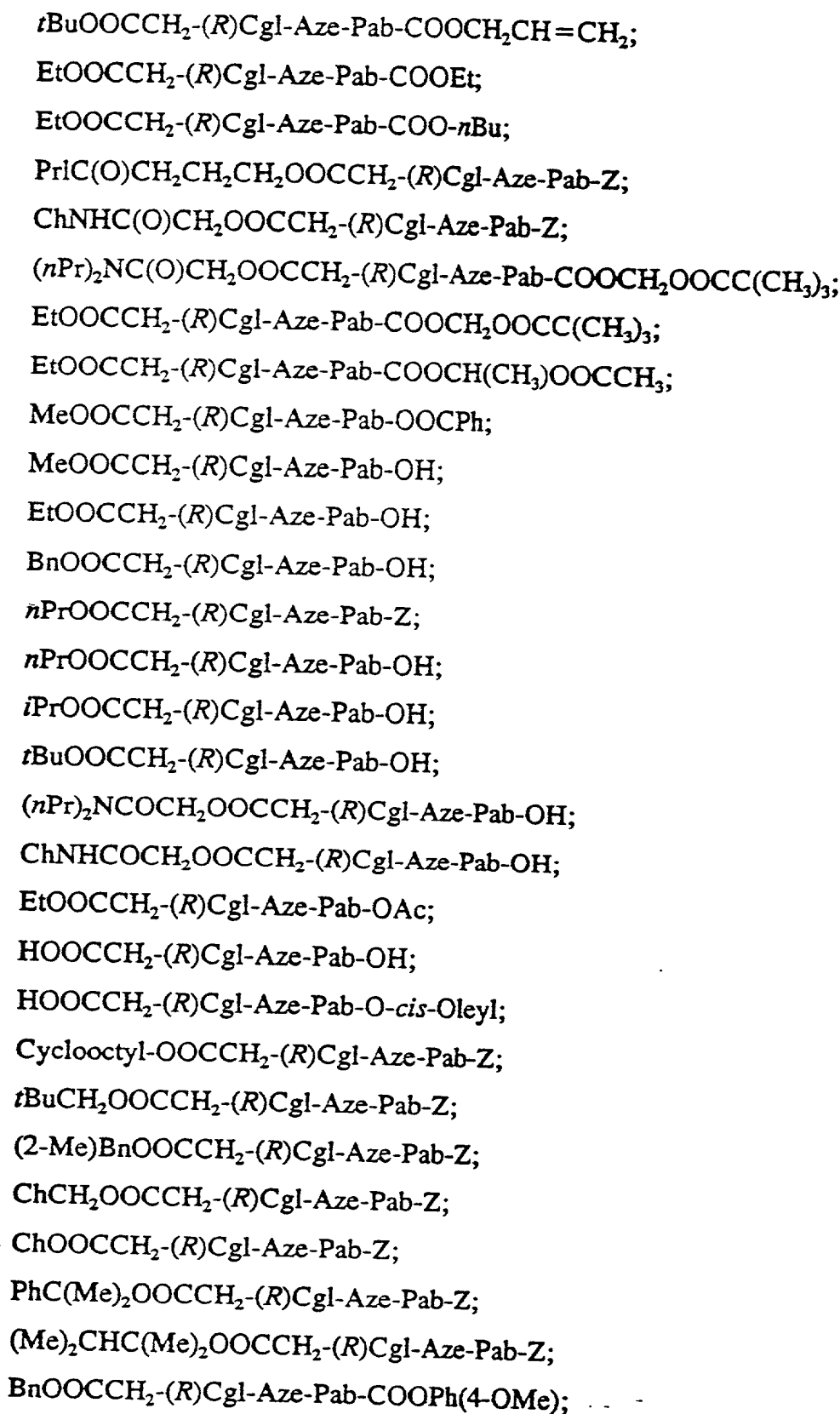
28. A compound as claimed in any one of the preceeding claims wherein, when R^2 represents $C(O)OR^7$ and R^7 represents optionally substituted phenyl, the optional substituent is selected from C_{1-6} alkyl, C_{1-6} alkoxy and halogen.

29. A compound as claimed in Claim 28 wherein the substituent is selected from methyl, methoxy and chloro.

30. A compound as claimed in any one of the preceeding claims wherein when R^2 represents $C(O)OR^7$ and R^7 represents optionally substituted C_{1-3} alkylphenyl, the optional substituent is nitro.

31. A compound as claimed in Claim 1 which is





$\text{ChCH}_2\text{OOCCH}_2\text{-(R)Cgl-Aze-Pab-COOPh(4-OMe)}$;
 $\text{(2-Me)BnOOCCH}_2\text{-(R)Cgl-Aze-Pab-COOPh(4-OMe)}$;
 $\text{EtOOCCH}_2\text{-(R)Cgl-Aze-Pab-COOPh(4-Me)}$;
 $\text{BnOOCCH}_2\text{-(R)Cgl-Aze-Pab-COOPh(4-Me)}$;
 $\text{BnOOCCH}_2\text{-(R)Cgl-Aze-Pab-COO-}n\text{Bu}$;
 $i\text{PrOOCCH}_2\text{-(R)Cgl-Aze-Pab-COOCH}_2\text{CH=CH}_2$;
 $\text{EtOOCCH}_2\text{-(R)Cgl-Aze-Pab-COO-}i\text{Bu}$;
 $\text{BnOOCCH}_2\text{-(R)Cgl-Aze-Pab-COO-}n\text{Pr}$;
 $\text{EtOOCCH}_2\text{-(R)Cgl-Aze-Pab-COOCH}_2\text{OOCCh}$;
 $\text{EtOOCCH}_2\text{-(R)Cgl-Aze-Pab-COOCH}_2\text{OOCCH}_2\text{Ch}$;
 $\text{EtOOCCH}_2\text{-(R)Cgl-Aze-Pab-COOCH(Me)OOCPh}$;
 $\text{EtOOCCH}_2\text{-(R)Cgl-Aze-Pab-COOCH}_2\text{OOCPh}$;
 $\text{BnOOCCH}_2\text{-(R)Cgl-Aze-Pab-COOCH(Me)OAc}$;
 $\text{EtOOCCH}_2\text{-(R)Cgl-Aze-Pab-COOCH}_2\text{OAc}$;
 $i\text{BuOOCCH}_2\text{-(R)Cgl-Aze-Pab-COOCH}_2\text{OAc}$;
 $\text{MeOOC-C(=CHEt)CH}_2\text{-OOCCH}_2\text{-(R)Cgl-Aze-Pab-Z}$;
 $\text{Men-OOCCH}_2\text{-(R)Cgl-Aze-Pab-COOPh(4-OMe)}$; and
 $\text{EtOOCCH}_2\text{-(R)Cgl-Aze-Pab-COOCH}_2\text{CCl}_3$.

32. A compound as claimed in Claim 1 which is

$\text{EtOOCCH}_2\text{-(R)Cgl-Aze-Pab-COOCH}_2\text{CCl}_3$;
 $\text{BnOOCCH}_2\text{-(R)Cgl-Aze-Pab-COOnBu}$;
 $n\text{PrOOCCH}_2\text{-(R)Cgl-Aze-Pab-Z}$;
 $\text{Cyclooctyl-OOCCH}_2\text{-(R)Cgl-Aze-Pab-Z}$;
 $\text{EtOOCCH}_2\text{-(R)Cgl-Aze-Pab-COOCH}_2\text{OOCCh}$;
 $\text{MeOOCCH}_2\text{-(R)Cgl-Aze-Pab-OH}$;
 $\text{EtOOCCH}_2\text{-(R)Cgl-Aze-Pab-OH}$;
 $n\text{PrOOCCH}_2\text{-(R)Cgl-Aze-Pab-OH}$;
 $i\text{PrOOCCH}_2\text{-(R)Cgl-Aze-Pab-OH}$;

BnOOCCH₂-(R)Cgl-Aze-Pab-OH; and
EtOOCCH₂-(R)Cgl-Aze-Pab-OAc.

33. A compound of formula I, as defined in Claim 1, with the additional proviso that R¹ does not represent -A¹C(O)OR⁴.

34. A compound of formula I, as defined in Claim 1, with the additional proviso that R⁴ and R⁵ do not independently represent H.

35. A compound of formula I, as defined in Claim 1, with the additional proviso R⁶ does not represent C₁₋₁₇ alkyl, when R² represents OC(O)R⁶.

36. A compound of formula I, as defined in Claim 1, wherein R¹ represents -A¹C(O)OR⁴.

37. A compound of formula I, as defined in Claim 1, wherein R⁴ and R⁵ independently represent H.

38. A compound of formula I, as defined in Claim 1, wherein R⁶ represents C₁₋₁₇ alkyl, when R² represents OC(O)R⁶.

39. A pharmaceutical formulation including a compound of formula I as defined in any one of Claims 1 to 38, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

40. A compound of formula I, as defined in any one of Claims 1 to 38, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

41. A compound of formula I as defined in any one of Claims 1 to 38, or

a pharmaceutically acceptable salt thereof, for use in the treatment of a condition where inhibition of thrombin is required.

42. A compound of formula I as defined in any one of Claims 1 to 38, or a pharmaceutically acceptable salt thereof, for use in the treatment of thrombosis.

43. A compound of formula I as defined in any one of Claims 1 to 38, or a pharmaceutically acceptable salt thereof, for use as an anticoagulant.

44. The use of a compound of formula I as defined in any one of Claims 1 to 38, or a pharmaceutically acceptable salt thereof as active ingredient in the manufacture of a medicament for the treatment of a condition where inhibition of thrombin is required.

45. The use as claimed in Claim 44, wherein the condition is thrombosis.

46. The use of a compound of formula I as defined in any one of Claims 1 to 38, or a pharmaceutically acceptable salt thereof, as active ingredient in the manufacture of an anticoagulant.

47. A method of treatment of a condition where inhibition of thrombin is required which method comprises administration of a therapeutically effective amount of a compound of formula I as defined in any one of Claims 1 to 38, or a pharmaceutically acceptable salt thereof, to a person suffering from, or susceptible to, such a condition.

48. A method as claimed in Claim 47, wherein the condition is thrombosis.

49. A method as claimed in claim 47, wherein the condition is hypercoagulability in blood and tissues.

50. The use of a compound of formula I, as defined in Claim 1 but without the provisos, as a prodrug.

51. A process for the preparation of compounds of formula I which comprises:

(a) for compounds of formula I in which R^2 represents OH, reaction of a corresponding compound of formula I, wherein R^2 represents $OC(O)R^6$ and R^6 is as defined in Claim 1 with an alkoxide base;

(b) for compounds of formula I in which R^2 represents OH, reaction of a corresponding compound of formula I wherein R^2 represents $C(O)OR^7$ and R^7 is as defined in Claim 1 with hydroxylamine, or an acid addition salt thereof;

(c) reaction of a corresponding compound of formula II,



wherein R^2 is as defined in Claim 1 with a compound of formula III,



wherein L^1 represents a leaving group and R^1 is as defined in Claim 1;

(d) for compounds of formula I in which R^1 represents H and R^2 represents OH or $C(O)OR^7$, reaction of a corresponding compound of formula I wherein R^1 represents C_{1-10} alkyl or C_{1-3} alkylphenyl, and R^2 represents OH or $C(O)OR^7$, with a base;

(e) for compounds of formula I wherein R^2 represents $OC(O)R^6$ and R^6 is as defined in Claim 1, reaction of a corresponding compound of formula I wherein R^2 represents OH, with a compound of formula IV,



or a compound of formula V,



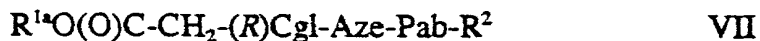
wherein Hal⁻ represents Cl or Br and, in both cases, R⁶ is as defined in Claim 1;

(f) for compounds of formula I in which R¹ represents H and R² represents OC(O)R⁶, and R⁶ is as defined in Claim 1, reaction of a corresponding compound of formula VI,



wherein P¹ represents an acid labile ester protecting group and R² represents OC(O)R⁶, wherein R⁶ is as defined in Claim 1, with an acid;

(g) for compounds of formula I in which R¹ represents R³, R³ represents C₁₋₁₀ alkyl or C₁₋₃ alkylphenyl, and R² represents OH or C(O)OR⁷, and R⁷ is as defined in Claim 1 by a trans-esterification of a corresponding compound of formula VII,



wherein R^{1a} represents a C₁₋₁₀ alkyl or C₁₋₃ alkylphenyl group other than that being formed, or an alternative labile alkyl substituent and R² is as defined in Claim 1.